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Phenotyping juvenile myoclonic epilepsy. Praxis induction as a biomarker of unfavorable prognosis

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ABSTRACT

Purpose: Juvenile myoclonic epilepsy (JME) is a heterogeneous syndrome with seizures presenting typical fluctuation in diurnal cycle and relation with awakening. Few publications have approached clinical expressions of praxis induction (PI) in the nosology of JME as well as its impact on outcome. The aim of this study is to characterize PI as the only reflex trait in JME and its relation with prognosis.
Method: JME with PI reported on a questionnaire and confirmed by video-EEG testing (Group 1, 20 patients) were compared with JME without any reflex epileptic trait (Group 2, 25 patients) and followed for a mean of 7.82 years (SD = 3.98). Circadian distribution and frequency of seizures were assessed in a diary. Patients also had psychiatric evaluation.
Results: Prevalence of PI was 20/133 (15%) JME patients, and was predominant in males (1.5 male: 1 female; OR 13; $p = 0.042$). Among Group 1 patients, only 2/20 presented seizures exclusively in the morning ($p = 0.013$), and none, exclusively on awakening ($p < 0.001$). PI patients had worse prognosis regarding control of myocloni ($p = 0.02$) and absences ($p = 0.01$); only 7/20 (35.0%) could be treated with VPA in monotherapy ($p = 0.01$). At the last follow-up, 2/20 (10.0%) of Group 1 and 10 (40.0%) of Group 2 patients were free of all three seizure types ($p = 0.02$). Even though relative risk of stress as a precipitant of seizures increased 3.82 times in Group 1, psychiatric comorbidities were not different between groups.
Conclusion: PI reflex trait in JME is related to seizures without preferential circadian occurrence and reduced response to antiepileptic drugs.

1. Introduction

Juvenile myoclonic epilepsy (JME) is the most common type of idiopathic generalized epilepsy (IGE); comprising 5–10% of all epilepsies [1]. The cardinal symptoms are myoclonic jerks of upper extremities; often precipitated by sleep deprivation [2,3]. Chronosensitivity is necessary for diagnosis. Occurrence of myoclonia exclusively on or after awakening and age of onset between 10 and 25 years are considered Class I diagnostic criteria while Class II comprises myoclonia occurring predominantly on or after awakening; sensitivity to visual stimuli; praxis induction (PI) and a wider 6–25 years range for onset of epilepsy [4]. Generalized tonic-clonic seizures (GTCS) are present in approximately 80–95% of patients and one third has absences [2]. Recently; data regarding long term prognosis of JME have been published [5–10]. Despite the recognition of some prognostic predictors such as presence of all three types of seizures; psychiatric comorbidity and drug resistance [10–13]; clinical diversity of JME is remarkable and the severity of the disorder itself has only rarely been analyzed [14–16].

PI, one of the four reflex epileptic traits that occur in JME, is defined as precipitation of seizures or epileptiform discharges (ED)

Abbreviations: NPP, neuropsychological protocol; ORM, orofacial reflex myocloni; PI, praxis induction.

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by complex, cognition-guided tasks, often involving visuomotor coordination and decision making [17–19]. Language and non-verbal triggers can be understood as mechanistically similar paradigms for seizure induction by verbal and non-verbal cognitive tasks [20,21]. Since in these patients seizures can be triggered by daily activities using their hands, the typical circadian distribution of seizures in JME would be lost [22].

Although Matsuoka et al. [14] in 1992 had recognized PI as a sign of worse prognosis in JME, few studies have approached its impact on JME outcome [16,23,24].

Moreover, there is no published prospective studies comparing JME patients with PI as the only reflex trait and JME patients without any reflex traits.

The aim of this study is to characterize PI as the only reflex trait in JME patients and its relation with prognosis.

2. Methods

2.1. Clinical evaluation

We used a semi-structured interview based on a questionnaire in order to endophenotype 133 JME patients according to their reflex epileptic traits. All had unequivocal diagnosis of JME based on electroclinical characteristics, including normal physical and neurological examinations, routine blood tests and brain imaging (CT/MRI) and generalized 4–6 Hz spike or polyspike-wave complexes, sometimes asymmetric, on a normal background in routine EEGs [25–27]. Inappropriate used AEDs encompassed carbamazepine, oxcarbazepine and phenytoin, as these are generally ineffective and might even aggravate seizures in JME. They were followed in the outpatient clinic of a tertiary center (Epilepsy Section, Department of Neurology and Neurosurgery, Universidade Federal de São Paulo, São Paulo, Brazil).

First, a clinical interview focused on myoclonic seizures occurrence and their circadian distribution (exclusively or predominantly on awakening, and the period of occurrence during the day) and a questionnaire regarding the precipitant factors including three questions were applied [23]: (a) Have you noticed any situations or states which do cause you to have more seizures?; (b) Can you identify some precipitating factor on this list: stress, sleep deprivation, specific thoughts/concentration, flashing lights, performing hand activities and complex finger manipulation, playing games, calculation, speaking in public, alcohol intake, playing musical instruments, listening to music, writing, dancing, drawing, menses, and others?; (c) Can you identify some factors or situations that would stop or inhibit your seizures?

Psychiatric comorbidity was then analyzed through Schedule Clinical Interview for DSM-IV, Axis I (SCID-I), and/or MINI [28] and State-Trait Anxiety Inventory (STAI), aiming to measure state (STAI-S) and trait (STAI-T) anxiety components [29].

2.2. Video-EEG

After obtaining informed consent, all 133 consecutive patients had a 4–6 h video-EEG monitoring, comprehending a research protocol approved by the Ethics Committee of our institution. Video-EEG was recorded on a digital equipment (Biologic 1, software Ceegraph 1) using the 10–20 International Electrode System, in addition to perioral and deltoid electrodes. For patients who had presented GTCS over the last 48 h, the protocol was postponed. Antiepileptic drugs (AEDs) were maintained in all patients. After having slept for at least 4 h, they had 30 min of awake EEG baseline recording, followed by a neuropsychological protocol (NPP), composed by tasks such as reading silently and aloud, talking, writing, performing mental and written calculations, drawing and spatial construction puzzles (for details, see Guaranha et al. [24]). The protocol and its analysis were based on criteria reported by Matsuoka et al. [20] and Mayer and Wolf [19]. PI tasks were performed at least 2 h after awakening. The sequence of tasks was administered randomly in different patients. PI was ascertained if at least one NPP task produced myoclonic seizures or ED activation (defined as ED per minute during NPP task at least the double of that in baseline EEG) [19,20]. Aiming to confirm true activation in case of none ED in the baseline, the task was applied again [24]. ED were classified as generalized or focal, and evaluated with respect to amplitude, using at least two montages. Bilateral anterior or posterior ED were not considered as focal abnormalities.

At the end of NPP, habitual activation methods as eye-closure, hyperventilation, intermittent photic stimulation, were performed.

2.3. Inclusion and exclusion criteria

Forty-five out of 133 JME patients were enrolled. Among them, two groups were selected: Group 1—JME with PI reported on questionnaire and confirmed by video-EEG NPP constituted by 20 (44.4%) patients and Group 2—JME without any reflex epileptic trait, by 25 (55.6%) patients. Three patients out of 20 (15%) included in Group 1 had language-induced orofacial reflex myocloni (ORM) in addition to PI [30]. Activation by other reflex traits, as photosensitivity/eye-closure sensitivity (40/133) or failure to confirm PI in NPP (7/133) were exclusion criteria. Patients who had presented photosensitivity/eye closure sensitivity on routine EEG (18/133) were also excluded as well as those with age less than 16 years (2/133), drugs/alcohol abuse intake and/or noncompliance (6/133), and less than a year of follow-up (15/133).

2.4. Follow-up

Seizure types and precipitant factors, AED therapy and treatment adherence were observed. Patients were oriented to avoid sleep deprivation and alcohol consumption. They received sodium valproate (VPA) as first choice drug, in mono or polytherapy and other AEDs considered reasonably effective in JME treatment, such as topiramate, lamotrigine, phenobarbital and benzodiazepines. Levetiracetam is not commercially available in our country. Doses and AEDs were chosen according to clinical response and adverse effects. Standard seizure calendars monitored seizure frequency. Myoclonia and absences were quantified as seizure days per month at the first clinical interview and currently. GTCS frequency per month was estimated at the first evaluation. GTCS frequency currently was the sum of all seizures occurred over the last year of follow-up. In addition, the total number of GTCS during life was estimated at the last evaluation.

Patients were followed-up for one to 15 years (mean 7.82 years; SD = 3.98).

3. Statistics

Comparisons between Groups 1 and 2 were performed by the nonparametric Mann–Whitney test for quantitative variables, the Fisher's exact test for qualitative variables, and the Student's *t*-test for the averages. The relation between PI reflex trait and the studied variables was estimated by odds ratio (OR). Demographic and clinical variables associated with PI reflex trait were calculated by multivariate logistic regression method. A p-value <0.05 was considered statistically significant.

4. Results

4.1. Demographics

Both groups were homogeneous regarding demographic data as gender, current age, age at epilepsy onset, duration of epilepsy, family history of epilepsy, and previous use of inappropriate AEDs (Table 1). It is worth mentioning that 7/20 Group 1 (35%) and 12/25 Group 2 (48%) patients were older than 30 years of age.

4.2. Questionnaire

Among the general precipitants of seizures, sleep deprivation was reported by 18/20 (90.0%) Group 1 patients and 23/25 (92.0%) of Group 2, and stress, by 15/20 (75.0%) and 11/25 (44.0%) of Groups 1 and 2, respectively ($p = 0.067$), with a relative risk of stress as a seizure precipitant of 3.82 times in Group 1 ($p = 0.039$; CI: 1.06–13.78). Other precipitant factors reported were alcohol intake, anxiety (one patient in each group, 5.0% and 4.0%, respectively), fasting (two patients of Group 1, 10.0%) and menses (two women of Group 2, 8.0%).

Among specific triggers, 12/20 (60.0%) Group 1 patients reported verbal tasks (writing, reading, speaking) and calculation; 3/20 had ORM during verbal tasks (15.0%); 17/20 (85.0%) spatial non-verbal tasks, performing precise and non-learned movements (5/17), playing musical instruments/learning rhythmic movements (4/17), working at computer (3/17), videogames (3/17) and board games (2/17). Stressful tasks, mainly involving decision-making, were the most efficient precipitant factors. Less commonly, tasks like dancing, swimming, cutting hair, painting, and sewing, precipitated seizures in 1/17 patients of Group 1, each.

4.3. Video-EEG findings

Nine patients (45%) of Group 1 and 19 (76%) of Group 2 were receiving AEDs in monotherapy, and the remaining in polytherapy, during video-EEG ($p = 0.015$). Voltage and frequency of interictal ED were higher in Group 1 ($p = 0.018$). At the baseline, 8/20 (40.0%) patients in Group 1 had focal ED in comparison with 1/25 (4.0%) in Group 2 ($p = 0.004$). We considered focal discharges those restricted to one cerebral region in general fronto-central or centro-parietal, which alternated between sides in interictal period. Tables 2 and 3 show NPP data. Interictal ED during PI tasks occurred in a frequency of 7.71 per minute in average (SD 15.01) with an average voltage of 41.8 μV. (SD 23.85). Ictal ED average voltage was 45.9 μV. (SD 43.62), and six patients (30%) had asymmetric ictal ED. There was no statistical difference between interictal and ictal average voltage.

4.4. Chronosensitivity

In patients with PI, the characteristic chronosensitivity of JME was largely lost (Fig. 1). Whereas all Group 2 patients, except two (23/25, 92.0%), had circadian distribution of seizures, it occurred in only 12/20 (60.0%) patients of Group 1 ($p = 0.011$; CI 95% 1.40–41.9; OR 7.67). Moreover, 13/25 (52.0%) of Group 2 patients had seizures occurring exclusively on awakening, in comparison with none of Group 1 ($p < 0.001$). Regarding the distribution of seizures over the day, while 21/25 (84.0%) of Group 2 patients had seizures exclusively in the morning, only 2/20 (10.0%) in Group 1 reported seizures always occurring at this period of the day.

4.5. Psychiatric comorbidity

There were no differences between groups in SCID I/MINI. STAI-S and STAI-T scores were similar in both ($p = 0.624$ and $p = 0.878$, respectively) (Table 4).

4.6. Treatment and outcome

Although at the first evaluation, both groups were similar in terms of all three seizure types, at the last, PI patients had worse prognosis regarding monthly control of myoclonic and absence seizures ($p = 0.02$ and $p = 0.01$, respectively). Only 2/20 patients (10%) in Group 1 were completely seizure free compared with 10/25 (40%) in Group 2 ($p = 0.023$). While VPA in monotherapy was used by 19/25 (76.0%) of Group 2 patients, 13/20 (65.0%) of Group 1 were in polytherapy ($p = 0.01$). VPA doses >1000 mg/day were necessary in 6/20 (31.6%) in Group 1, in comparison with 4/25 (16.7%) in Group 2 ($p = 0.295$). Finally, there were no statistical differences with respect to GTCS control in the last year of

Table 1
Demographic data.

	JME with praxis induction trait	JME without any reflex trait	*p*-Value
N	20	25	
Gender (females)	8 (40%)	14 (56%)	*0.373
Age (average; SD)	30.5 y; 8.86 y	33.4 y; 10.59 y	**0.385
19–30 y	13 (65.0%)	13 (52.0%)	**0.713
31–40 years	4 (20.0%)	6 (24.0%)	
>41 years	3 (15.0%)	6 (24.0%)	
Age at epilepsy onset (average; SD)	14.3 y; 3.70 y	13.2 y; 3.28 y	**0.395
Duration of epilepsy (average; SD)	16.7 y; 8.70 y	20.2 y; 10.86 y	**0.243
Follow-up (average; SD)	6.7 y; 4.13 y	9.1 y; 3.59 y	**0.05
Diagnosis delay (average; SD)	9.1 y; 8.36 y	11.2 y; 9.10 y	**0.499
Epilepsy in family	12 (60.0%)	12 (48.0%)	*0.55
First grade	7 (35.0%)	4 (16.0%)	**0.375
Second grade	5 (25.0%)	8 (32.0%)	
Previous inappropriate AEDs use	17 (85.0%)	14 (56.0%)	*0.054

AEDs: antiepileptic drugs; JME: juvenile myoclonic epilepsy, SD: standard deviation. Previous inappropriate AEDs use: carbamazepine, oxcarbazepine and phenytoin.
* Fisher's exact test.
** Student's *t*-test.

Table 2
Epileptiform discharges at baseline and with non-specific activators.

	JME with praxis induction trait (Group 1)	JME without any reflex trait (Group 2)	*p*-Value
In monotherapy at video-EEG	9 (45%)	19 (76%)	0.015
In polytherapy at video-EEG	11 (55%)	6 (24%)	
ED at baseline	13 (65%)	6 (24%)	0.008
Focal ED at baseline	8 (40.0%)	1 (4.0%)	0.004
EDF at baseline (average/min; SD)	0.43; 1.003	0.14; 0.425	0.004
ED voltage (average μV; SD)	37.8; 33.97	16.4; 33.65	0.018
ED at sleep	10 (50%)	9 (36%)	0.761
EDF at sleep (average/min; SD)	0.71; 1.30	0.41; 0.847	0.309
ED at hyperventilation	9 (45%)	6 (24%)	0.205
EDF at hyperventilation (average/min; SD)	1.19; 3.779	0.50; 1.358	0.238

ED: epileptiform discharges; EDF: epileptiform discharges frequency, SD: standard deviation.
* Fisher's exact test.

Table 3
Specific tasks inducing epileptiform discharges and/or seizures. Number of affected patients, paroxysms rate and voltage.

Tasks inducing ED/seizures	1 task	9 (45.0%)
	2 tasks	4 (20.0%)
	3 tasks	3 (15.0%)
	>3 tasks	4 (20.0%)
Non verbal tasks	Pyramid	11(55.0%)
	Rubik	6 (30.0%)
	Conundrum	6 (30.0%)
	Drawing	5 (25.0%)
	Picture reproduction	3 (15.0%)
	Other puzzles	5 (25.0%)
Verbal tasks	Writing	3 (15.0%)
	Reading	1 (5.0%)
	Talking	1 (5.0%)
Calculation	Written calculation	1 (5.0%)
	Mental calculation	1 (5.0%)
Interictal ED	Interictal ED occurrence on PI)	18 (90%)
	Interictal ED/min on PI (average; SD)	2.16; 3.875
ED on PI tasks	Total ED/min on PI (average; SD)	7.71; 15.011
	ED voltage (μV) on PI (average; SD)	41.8; 23.85
	Focal ED during PI	8 (40%)
Ictal ED	Ictal ED occurrence on PI	14 (70%)
	Ictal ED voltage (μV) on PI (average; SD)	45.9; 43.62
	assymetric ictal ED	6 (30.0%)
Arm myoclonia	Bilateral myoclonia	4 (16%)
	Left arm myoclonia	7 (28%)
	Right arm myoclonia	7 (28%)
Perioral myoclonia	Bilateral perioral myoclonia	1 (5.0%)
ED mental calculation	ED mental calculation	5 (25%)
	ED mental calculation voltage (average; SD)	0.91; 3.790
ED speaking and writing	ED speaking, writing	11 (55%)
	ED speaking, writing voltage (average; SD)	1.42; 3.915
ED reading silently	ED reading silently	4 (20%)
	ED reading silently voltage (μV) (average; SD)	0.13; 0.324
ED reading aloud	ED reading aloud	4 (20%)
	ED reading aloud voltage (μV) (average; SD)	0.93; 3.019

ED: epileptiform discharges; SD: standard deviation.

follow-up between groups ($p = 0.32$), as well as lifelong GTCS occurrence ($p = 0.56$) (Table 4 and Fig. 2).

4.7. PI and quality of life

The occurrence of seizures triggered by leisure activities led patients to stop practicing them. Furthermore, different reasons have obliged 6/20 (30.0%) patients with PI to abandon their occupations, such as a hairdresser, for being unable to cut the hair of his customers and a cook, who was repeatedly fired because of accidents while cooking. Moreover, trying to learn skills for new professions was also difficult, since during motor learning, the risk of having PI seizures was considerable. The provocation of myoclonia in turn caused concerns by the threat of a GTCS.

5. Discussion

In the earlier literature, specific terms, such as playing chess, card and other games, calculation, writing, drawing and decision making were used to report that complex tasks could trigger epileptic seizures. Since the proposal of Inoue et al. [18] all these terms were included in the comprehensive concept of PI [17]. Prevalence of PI in JME is variable around the world, from 24 to 84% [17,31]. It is intriguing that PI in JME is significantly more frequent in Japanese (46.7–84%) [20,31] than in Brazilian patients (38%) [24]. An explanation could be a difference in precipitating tasks. Whereas in our patients, calculation was rarely effective (Table 3), in the meta analysis of 72 patients by Inoue et al. [18] calculation was the most common precipitating task. Probably, in Japan, the common use of the Soroban, the Japanese abacus, which requires fine and complicated movements to perform calculations, allowed the witness by Japanese epileptologists of this under-reported daily seizure activation trait [32]. Among the possible reasons for this long hiatus to define relation between PI and JME, as well as its impact in JME nosology is that documentation of this trait requires prolonged video-EEG studies, far from routine EEGs, in which only the traditional activation methods, such as hyperventilation and photic stimulation, are used.

In this prospective study, we investigated the influence of PI in JME endophenotypes and prognosis with a mean follow-up of 7.82 years. After submitting 133 JME patients to a semi-structured questionnaire and video-EEG NPP, only 20 (15%) had PI as the only reflex trait.

Although Matsuoka et al. [14] had already reported the negative impact of PI at the beginning of treatment in 9/32 (28%) JME patients, who continued having seizures 20 to 39 years despite treatment, this reflex trait has not been considered in the several recent series dealing with JME long term prognosis [5–10]. In Matsuoka's series, these patients, besides more focal ED on EEG, had stronger response to NPP from the epilepsy onset. The authors suggested that PI would be a predictor of prognosis in JME and that the severity of disease process itself, rather than psychosocial factors, might be crucial to determine its long-term course [14]. Since then, other Japanese authors confirmed that PI is indicative of unfavorable prognosis in patients with JME [18,33]. Our study comparing prospectively followed JME patients with and without PI confirms these findings. We also confirm the observation of Matsuoka et al. [14] regarding higher number of focal ED, since focal interictal ED were present in 40.0% and 4.0% of Group 1 and 2 patients, respectively ($p = 0.004$).

Video-EEG NPP investigation showed that 3/20 patients of this series had both, limb myoclonia and ORM, occurring independently, triggered by specific tasks. They were included as PI since perioral muscles are the effectors of cortical networks processing language [34]. Mayer et al. [35] postulated that in this case primary motor areas were one of the components of a hyperexcitable physiological cortico-subcortical circuitry providing a functional link for the observation of seizures triggered by reading in JME. Triggering seizures with the use of hands seems obvious since patients with JME present increased motor cortical excitability [36].

PI affects significantly the quality of life of JME patients, in terms of professional and leisure activities. Learning new skills involving the use of hands increases the amount of decision making in a visuomotor performance, which seems to be central to PI.

In the present series we confirm the male predominance of PI in JME (1.5 male: 1 female; OR 13; $p = 0.042$) suggested in other series of PI (ratios 3:1 and 2.3:1) [22,31] and the long lasting expression of the trait, since 7/20 (35%) still expressed PI beyond the fourth decade of life. In two JME patients described by Matsuoka et al., PI under a continuous identical drug regimen persisted up to the fifth decade of life despite decrease of spontaneous myoclonic seizures, suggesting that seizure propensity of JME improves over time but PI persists longer [37]. Therefore, this trait appears to be dissimilar to photosensitivity, which may disappear spontaneously around the middle of the third decade of life in JME patients [38].

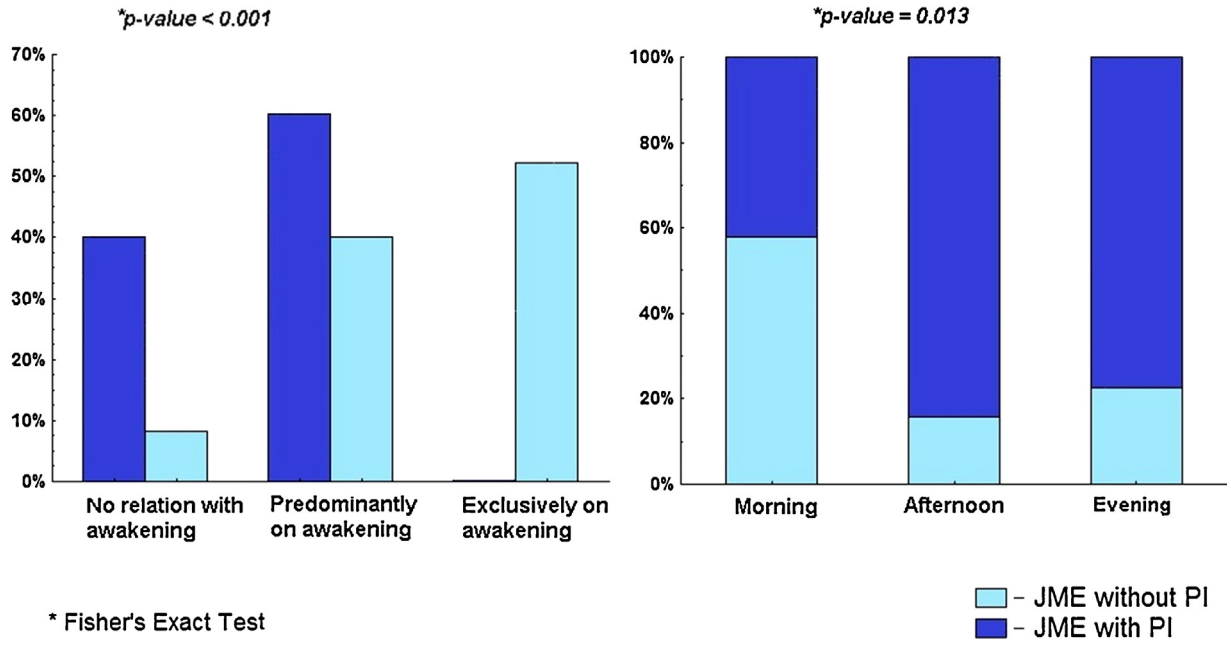

Fig. 1. Relation between myoclonic seizures and awakening and distribution of myoclonic seizures over the periods of the day in patients with JME with praxis induction and in JME patients without any reflex trait.

5.1. Chronosensitivity

No JME patient with PI presented seizures exclusively on awakening, and only 2/20 presented seizures exclusively in the morning. This finding means that chronodependency, one of the hallmarks of JME expressed by myoclonic jerks in early morning, is lost in patients with PI. Goossens et al. [22] stated that patients with PI had the clinical picture dominated by reflex activation and this could be probably responsible for the absence of fluctuation with diurnal cycle differing from JME patients. This was a possible consideration in the discussion of that article, objectively verified in our work for the first time.

5.2. Response to treatment

Previously, our group reported that only 25/65 JME patients (38.5%) became completely seizure free for at least three years if mild and isolated absences or myoclonia were considered [24].

Table 4
Prognosis regarding seizure control and antiepileptic drugs.

		JME with PI trait	JME without any reflex trait	*p*-Value
N		20	25	
Seizure types	Myoclonia/month (average; SD) at epilepsy onset	17.6; 13.27	11.2; 11.59	**0.18
	Myoclonia freedom currently	2 (10.0%)	14 (56.0%)	*0.002
	Myoclonia/month (average; SD) currently	1.8; 0.77	1.4; 0.76	**0.023
	Absences at epilepsy onset	10 (50.0%)	8 (32.0%)	**0.241
	Absences/month (average; SD) at epilepsy onset	12.1; 12.80	9.5; 12.69	**0.673
	Absences freedom currently	17 (85.0%)	21 (84.0%)	*0.327
	Absences/month (average; SD) currently	6.2; 8.09	2.6; 6.30	**0.01
	GTCSs/month (average; SD) at epilepsy onset	0.986; 0.733	0.982; 0.751	**0.493
	GTCSs over the last year (average; SD)	1.2; 1.39	1.0; 1.63	**0.378
	GTCSs freedom currently	9 (45.0%)	16 (64.0%)	*0.239
	GTCSs lifelong (average; SD)	19.2; 16.16	18.1; 22.51	**0.564
	GTCSs lifelong > 20	6 (30.0%)	8 (12.0%)	**0.019
	GTCSs lifelong 11–20	5	8 (12.0%)	**0.04
	Myoclonia, absences and GTCSs freedom	2(10.0%)	10 (40.0%)	*0.023
AEDs	Patients on AEDs	20 (100.0%)	25 (100.0%)	1.0
	AEDs monotherapy	7 (35.0%)	19 (76.0%)	*0.001
	Valproate use	19 (95.0%)	24 (96.0%)	1.0
	Valproate >1000 mg/day	6 (31.6%)	4 (16.7%)	**0.295
	Phenobarbital	5 (13.9%)	2 (5.6%)	**0.214
	Lamotrigine	5 (13.9%)	4 (11.1%)	**0.482
	Topiramate	3 (8.3%)	1 (2.8%)	**0.475
	Benzodiazepines	3 (8.3%)	4 (16.0%)	**0.309
Psychiatric disorders	Psychiatric diagnosis	9 (45.0%)	9 (36.0%)	*0.559
	Mood disorders	6 (30.0%)	7 (28.0%)	**0.895
	Psychotic disorders	2 (10.0%)	1 (4.0%)	

AEDs: antiepileptic drugs; GTCSs: generalized tonic-clonic seizures, SD: standard deviation.
* Fisher's exact test.
** Student's *t*-test.

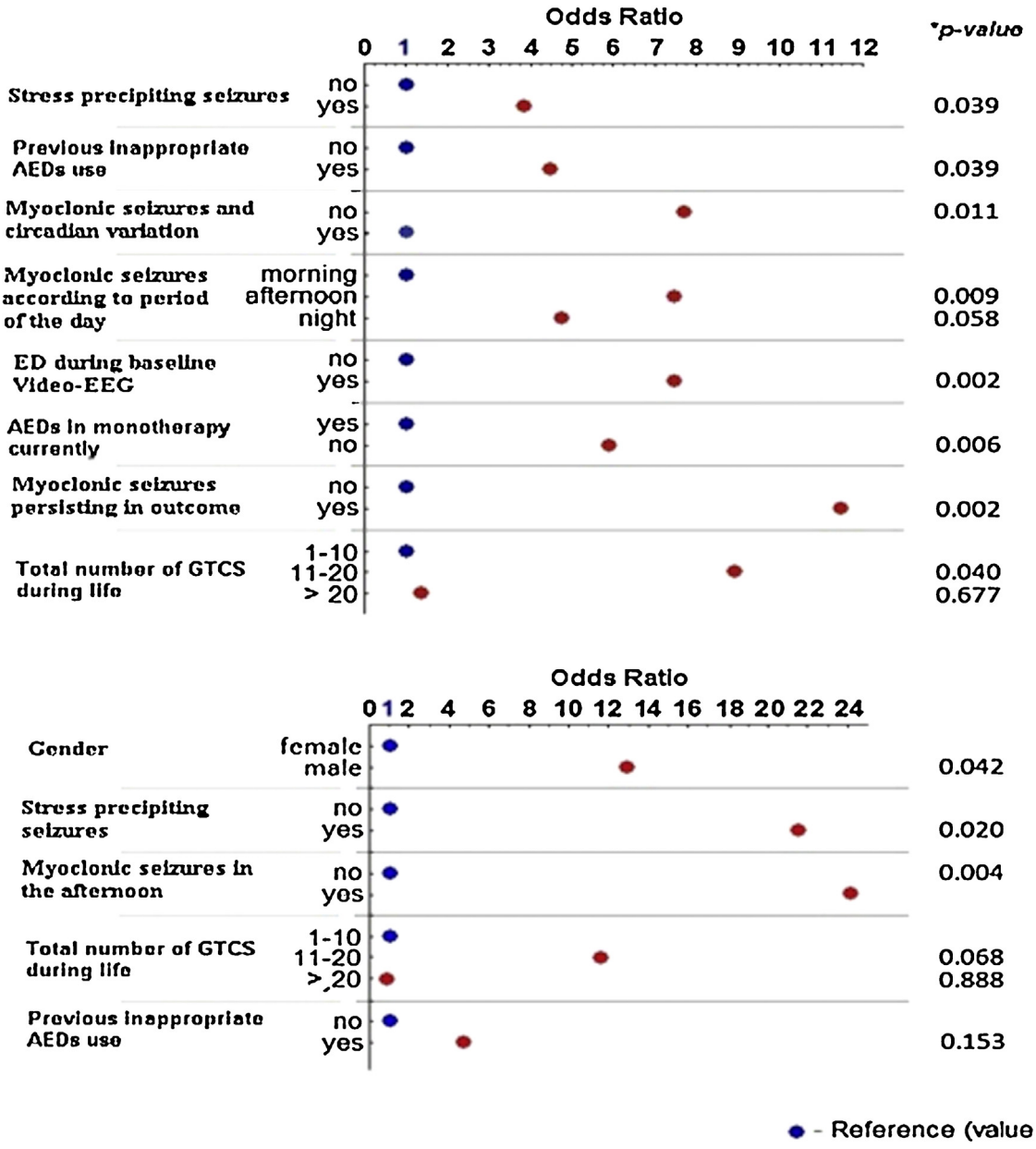

Fig. 2. Univariate and multivariate analyses of variables with significant increased risk in patients with JME and praxis induction. AEDs: antiepileptic drugs; GTCS: generalized tonic-clonic seizures.

This percentage of seizure free patients is similar to the 31% (54/175) of patients whose seizures were completely controlled, between the second and the fifth years, in data recently reporting larger series including the use of all available AEDs such as levetiracetam and zonisamide [10]. In Guaranha's series, longer epilepsy duration (13.9 ± 9.0 *vs.* 8.7 ± 8.2; $p = 0.019$); higher prevalence of the combination of all three seizure types (72.0% *vs.* 30.0%; $p = 0.003$); discharges in baseline EEG (56.0% *vs.*22.5%; $p = 0.008$); seizure recording (68% *vs.* 20%; $p < 0.001$) and sensitivity to praxis (63.6% *vs.* 29.6%; $p = 0.023$) were factors linked to worse prognosis [24]. Recent studies, in quite heterogeneous series, varying from community-based to tertiary centers, have demonstrated variable rates of pharmacoresistance: 13%, in a population-based series [6] 15.5–30.0% in outpatient clinics [39,40].

In this current series of JME patients with documented PI as the only reflex trait, in comparison with JME patients without any reflex trait, we confirm that PI determines worse prognosis for control of myoclonia and absences, resulting in the need of AEDs in polytherapy. However, neither GTCS frequency nor the total number of GTCS during life was increased in JME with PI.

Although stress has been reported as a common precipitant of seizure in JME with PI, in this series it increased 3.82 times the relative risk for seizures. Psychiatric comorbidities in general and anxiety itself as measured by STAI, did not prevail in patients with PI.

The limitations of this study are the considerable interval between the onset of epilepsy and the first evaluation in Groups 1 (average = 9.1 years, SD = 8.36 years) and 2 (average = 11.2 years, SD = 9.10 years), respectively, partly due to the delay to define syndromic diagnosis, and hence, not appropriate AEDs intake at the onset of epilepsy; all patients were followed in a tertiary center of epilepsy, which may not represent the actual JME population.

6. Conclusions

JME is a syndrome with significant endophenotypes. PI reflex trait, present in about one-fifth of patients, is related to seizures

without preferential circadian occurrence that increases significantly the burden of epilepsy. Questionnaires and/or video-EEG recordings can identify PI early at epilepsy onset. PI patients have increased ED in baseline EEG and more frequently focal ED. Even though relative risk of seizure precipitation by stress is increased in PI, this reflex trait is not related with psychiatric comorbidities, but with reduced response to AEDs.

Conflict of interest statement

None of the authors has any conflict of interest to disclose. We affirm that this report is consistent with the guidelines on issues involved in ethical publication of Seizure.

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References

[1] Jallon P, Latour P. Epidemiology of idiopathic generalized epilepsies. Epilepsia 2005;46(Supp. l):S10–4.
[2] Genton P, Thomas P, Kasteleijn-Nolst Trenité DG, Medina MT, Salas-Puig J. Clinical aspects of juvenile myoclonic epilepsy. Epilepsy Behav 2013;28(Suppl. 1):S8–14.
[3] Camfield CS, Striano P, Camfield PR. Epidemiology of juvenile myoclonic epilepsy. Epilepsy Behav 2013;28(Supp. l):S15–7.
[4] Kasteleijn-Nolst Trenité DG, Schmitz B, Janz D, Delgado-Escueta AV, Thomas P, Hirsch E, et al. Consensus on diagnosis and management of JME: from founder's observations to current trends. Epilepsy Behav 2013;28(Suppl. 1):S87–90.
[5] Baykan B, Altindag EA, Bebek N, Ozturk AY, Aslantas B, Gurses C, et al. Myoclonic seizures subside in the fourth decade in juvenile myoclonic epilepsy. Neurology 2008;70:2123–9.
[6] Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: a population-based study. Neurology 2009;73:1041–5.
[7] Geithner J, Schneider F, Wang Z, Berneiser J, Herzer R, Kessler C, et al. Predictors for long-term seizure outcome in juvenile myoclonic epilepsy: 25–63 years of follow-up. Epilepsia 2012;53:1379–86.
[8] Senf P, Schmitz B, Holtkamp M, Janz D. Prognosis of juvenile myoclonic epilepsy 45 years after onset: seizure outcome and predictors. Neurology 2013;81:2128–33.
[9] Syvertsen MR, Thuve S, Stordrange BS, Brodtkorb E. Clinical heterogeneity of juvenile myoclonic epilepsy: follow-up after an interval of more than 20 years. Seizure 2014;23:344–8.
[10] Hofler J, Unterberger I, Dobesberger J, Kuchukhidze G, Walser G, Trinka E. Seizure outcome in 175 patients with juvenile myoclonic epilepsy. A long-term observational study. Epilepsy Res 2014;108:1817–24.
[11] Gelisse P, Thomas P, Samuelian JC, Genton P. Psychiatric disorders in juvenile myoclonic epilepsy. Epilepsia 2007;48:1032–3.
[12] Trinka E, Kienpointner G, Unterberger I, Luef G, Bauer G, Doering LB, et al. Psychiatric comorbidity in juvenile myoclonic epilepsy. Epilepsia 2006;47:2086–91.
[13] De Araujo Filho GM, Rosa VP, Lin K, Caboclo LO, Sakamoto AC, Yacubian EM. Psychiatric comorbidity in epilepsy: a study comparing patients with mesial temporal sclerosis and juvenile myoclonic epilepsy. Epilepsy Behav 2008;13:196–201.
[14] Matsuoka H. The seizure prognosis of juvenile myoclonic epilepsy. Jpn J Psychiatry Neurol 1992;46:293–6.
[15] Martinez-Juarez IE, Alonso ME, Medina MT, Duron RM, Bailey JN, Lopez-Ruiz M, et al. Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up. Brain 2006;129:1269–80.
[16] Guaranha MS, de Araujo Filho GM, Lin K, Guilhoto LM, Caboclo LO, Yacubian EM. Prognosis of juvenile myoclonic epilepsy is related to endophenotypes. Seizure 2011;20:42–8.
[17] Yacubian EM, Wolf P. Praxis induction. Definition, relation to epilepsy syndromes, nosological and prognostic significance. A focused review. Seizure 2014;23:247–51.
[18] Inoue Y, Seino M, Kubota H, Yamakaku K, Tanaka M, Yagi K. Epilepsy with praxis-induced seizures. In: Wolf P, editor. Epileptic seizures and syndromes. London: John Libbey; 1994. p. 81–91.
[19] Mayer T, Wolf P. Perioral reflex myoclonias in reading epilepsy and juvenile myoclonic epilepsy. In: Wolf P, Inoue Y, Zifkin B, editors. Reflex epilepsies: progress in understanding. London: John Libbey; 2004. p. 57–70.
[20] Matsuoka H, Takahashi T, Sasaki M, Matsumoto K, Yoshida S, Numachi Y, et al. Neuropsychological EEG activation in patients with epilepsy. Brain 2000;123:318–30.
[21] Ferlazzo E, Zifkin BG, Andermann E, Andermann F. Cortical triggers in generalized reflex seizures and epilepsies. Brain 2005;128:700–10.
[22] Goossens LA, Andermann F, Andermann E, Remillard GM. Reflex seizures induced by calculation, card or board games, and spatial tasks: a review of 25 patients and delineation of the epileptic syndrome. Neurology 1990;40:1171–6.
[23] Da Silva Sousa P, Lin K, Garzon E, Sakamoto AC, Yacubian EM. Self-perception of factors that precipitate or inhibit seizures in juvenile myoclonic epilepsy. Seizure 2005;14:340–6.
[24] Guaranha MS, da Silva Sousa P, de Araujo Filho GM, Lin K, Guilhoto LM, Caboclo LO, et al. Provocative and inhibitory effects of a video-EEG neuropsychologic protocol in juvenile myoclonic epilepsy. Epilepsia 2009;50:2446–55.
[25] Janz D. Epilepsy with impulsive petit mal (juvenile myoclonic epilepsy). Acta Neurol Scand 1985;72:449–59.
[26] Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389–99.
[27] Lancman ME, Asconape JJ, Penry JK. Clinical and EEG asymmetries in juvenile myoclonic epilepsy. Epilepsia 1994;35:302–6.
[28] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl. 20):S22–33.
[29] Biaggio AMB, Natalicio L, Spielberger C. Desenvolvimento da forma experimental em português do Inventário de Ansiedade Traço-Estado de Spielberger. Arq Bras Psicol Aplicada 1977;29:31–44.
[30] Yacubian EMT, Wolf P. Orofacial reflex myocloni. Definition, relation to epilepsy syndromes, nosological and prognosis significance. A focused review. Seizure 2015;30:1–5.
[31] Matsuoka H, Takahashi T, Sato M. The clinical and electroencephalographic studies of juvenile myoclonic epilepsy. Jpn J Psychiatry Neurol 1988;42:556–7.
[32] Yamamoto J, Egawa I, Yamamoto S, Shimizu A. Reflex epilepsy induced by calculation using a "Soroban," a Japanese traditional calculator. Epilepsia 1991;32:39–43.
[33] Inoue Y, Kubota H. Juvenile myoclonic epilepsy with praxis-induced seizures. In: Schmitz B, Sander T, editors. Juvenile myoclonic epilepsy: the Janz syndrome. Petersfield: Wrightson Biomedical; 2000. p. 73–81.
[34] Salek-Haddadi A, Mayer T, Hamandi K, Symms M, Josephs O, Fluegel D, et al. Imaging seizure activity: a combined EEG/EMG-fMRI study in reading epilepsy. Epilepsia 2009;50:256–64.
[35] Mayer TA, Schroeder F, May TW, Wolf PT. Perioral reflex myoclonias: a controlled study in patients with JME and focal epilepsies. Epilepsia 2006;47:1059–67.
[36] Woermann FG, Free SL, Koepp MJ, Sisodiya SM, Duncan JS. Abnormal cerebral structure in juvenile myoclonic epilepsy demonstrated with voxel-based analysis of MRI. Brain 1999;122:2101–8.
[37] Matsuoka H, Takahashi T, Sasaki M, Yoshida S, Numachi Y, Sato M. The long-term course of seizure susceptibility in two patients with juvenile myoclonic epilepsy. Seizure 2002;11(2):126–30.
[38] Jeavons PM, Bishop A, Harding GFA. The prognosis of photosensitivity. Epilepsia 1986;27(5):569–75.
[39] Fernando-Dongas MC, Radtke RA, VanLandingham KE, Husain AM. Characteristics of valproic acid resistant juvenile myoclonic epilepsy. Seizure 2000;9(6):385–8.
[40] Genton P, Gelisse P. Juvenile myoclonic epilepsy. Arch Neurol 2001;58(9):1487–90.